Attorney Docket No. O/99469 US

REMARKS

Upon entry of the above amendment claims 1, 3-11 and 13-16 will be pending in the instant application. Claim 13 has been withdrawn due to a restriction requirement. Applicants have amended the claims to better reflect what Applicants consider their invention. Applicants have not raised any issue of new matter.

Applicants would like to thank the Examiner for the Interview of July 17, 2003. Applicants found the Interview informative and productive.

Priority

Applicants acknowledge that the Examiner has reported that **SOME** of the certified copies of the priority documents have been received in the January 15, 2002 Office Action. The July 11, 2003 Office Action does not indicate an acknowledgement for priority. Applicants respectfully request the Examiner to identify what copies are present in the file and what copies are not present.

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Issue Under 35 U.S.C. §103(a)

Claims 1, 3-6, 8-11 and 14-16 stand rejected under 35 U.S.C. §103(a) as allegedly being obvious over Bardin '834 (USP 5,342,834). Applicants respectfully submit that patentable distinction exist between the present invention and the cited prior art.

Distinctions Between the Present Invention and Bardin '834

Bardin '834 discloses similar compounds (7α-methyl), whereas the claimed compounds are (C_2) alkyl. The Examiner asserts that column 7, lines 9-14 of Bardin '834 provides motivation to modify Bardin '834.

As discussed in previous responses, Bardin '834 discloses a method of providing androgen supplementation without inducing an abnormal weight gain in the prostrate. *See column 1, lines 11-13.* Bardin '834 only discloses intramuscular, subcutaneous or transdermal administration. See claim 8.

Bardin '834 fails to disclose the 7α-ethyl compound. Bardin '834 fails to address the oral activity of the compounds.

Applicants emphasize that the present invention provides orally active androgens. Bardin '834 fails to provide motivation to a skilled artisan to modify the disclosure of Bardin '834 to make the present invention as described in the present claims.

Applicants respectfully request withdrawal of the 35 U.S.C. §103(a) rejection.

Unexpected Results

If the Examiner is still not persuaded that a *prima facie* case of obviousness has not been established, Applicants have previously submitted a 37 C.F.R. §1.132 Declaration by Dr. M.E. De Gooijer.

Regarding Bardin '834

The submitted data show that a change in the stereochemistry at the 7 position imparts an unexpected change in the oral activity effect of the compounds in this field. Inspecting the comparison of MENT with 7β-methyl nandrolone or 7α-vinyl nandrolone with 7β-vinyl nandrolone (Table 1), one can see the major improvement in androgen receptor activation by selecting the 7α stereoconfiguration.

The present specification addresses this unexpected result on page 1, lines 13-15 by reciting, "[a] more potent androgen is 7a-methyl-19-nortestoterone (MENT) disclosed in FR 4,521 M and US 5,342,934. An important drawback of MENT, however, is its unfavorable kinetics which limits its use as an orally active

androgen." Also on page 5, lines 10-12, Applicants recite tat the present invention has better oral activity than MENT in Bardin '834

Applicants disclose the importance of selection of a substituent length of more than one carbon atom at position 7 of the nandrolone skeleton. This skeleton is also named 19-nortestosterone or 17β-hydroxy-estr-4-en-3-one.

The effect is illustrated by comparison of MENT with 7α-ethyl-nandrolone (Table 2). This is also done in the patent specification on page 25 and 26, wherein Example 1 is 7α-ethyl-nandrolone. Although some activity is lost in the in vitro androgen receptor assay, there is higher activity by oral administration.

Table 2

A: Androgen receptor activity (data from declaration)
B: Metabolic stability $t_{1/2}$ (min) with human hepatocytes (data from specification)
C: ED_{50} in mg/kg p.o. in LH suppression assay (data from specification)

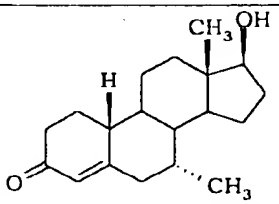
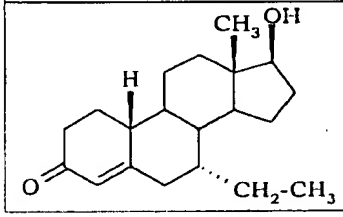
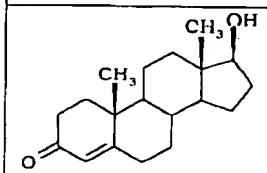
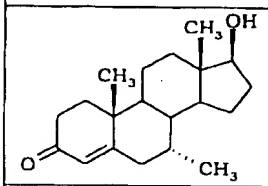
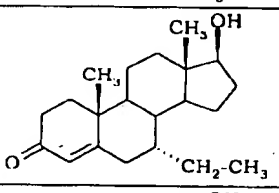
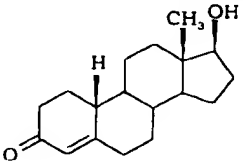
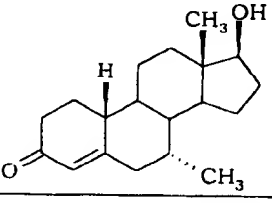
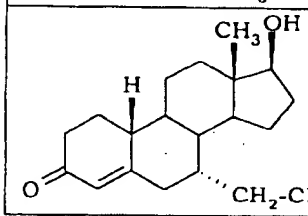
Compound structure	Compound name	*Measurement results*		
		A	*B*	*C*
	7α-methyl nandrolone; MENT; 7α-methyl-19-nortestosterone	269%	20 min	10
	7α-ethyl-nandrolone (7α-ethyl, 17β-hydroxy estr-4-en-3-one)	152%	48 min	2.5

Table 2 clearly shows a comparison of the disclosed compound in Bardin '834 and the present invention with a (C_2)alkyl at the 7α position. Applicants respectfully submit that Table 2 shows different activity of the two 19-nortestosterone (nandrolone) analogs. Thus, a skilled artisan would have not have expected the comparison to generate such results. Thus, the superior results shown in Table 3 and the accompanying §132 declaration would be unexpected to a skilled artisan.

Table 3

A: Androgen receptor activity (data from declaration)
B: Metabolic stability $t_{1/2}$ (min) with human hepatocytes (data from specification supplemented with data from declaration)
C: ED_{50} in mg/kg p.o. in LH suppression assay (data from specification)

Compound structure	Compound name	*Measurement results*		
		A	*B*	*C*
	testosterone	16.5 %	15 min	
	7α-methyl-testosterone	45%		
	7α-ethyl-testosterone; Compound 2 in Solo et al	No in house data available		
	nandrolone (19-nortestosterone	55%	16 min	
	7α-methyl nandrolone; MENT; 7α-methyl-19-nortestosterone	269%	20 min	10
	7α-ethyl-nandrolone (7α-ethyl, 17β-hydroxy estr-4-en-3-one)	152%	48 min	2.5

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Applicants respectfully submit that the unexpected activity is in reference to oral activity. Applicants respectfully request withdrawal of both 35 U.S.C. §103(a) rejection in light of the unexpected results discussed above and in the attached §132 declaration.

Conclusion

Applicants submit that every issue raised by the outstanding Office Action has been addressed and rebutted. Therefore, the present claims define patentable subject matter and are in condition for allowance.

Should the Examiner believe that a conference would be helpful in advancing the prosecution of this application, he is invited to telephone Applicants' Attorney at the number below.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2334 for any

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additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

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Cover sheet

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October 13, 2003

16...pages including cover sheet.

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RE: USSN 09/937,274
Attorney Docket Number 99469 US
Response to Final Office Action of July 11, 2003

Please accept the document that follows in the above-identified application:

Amendment Under 37 C.F.R. § 1.116 (15 pages)

Intervet